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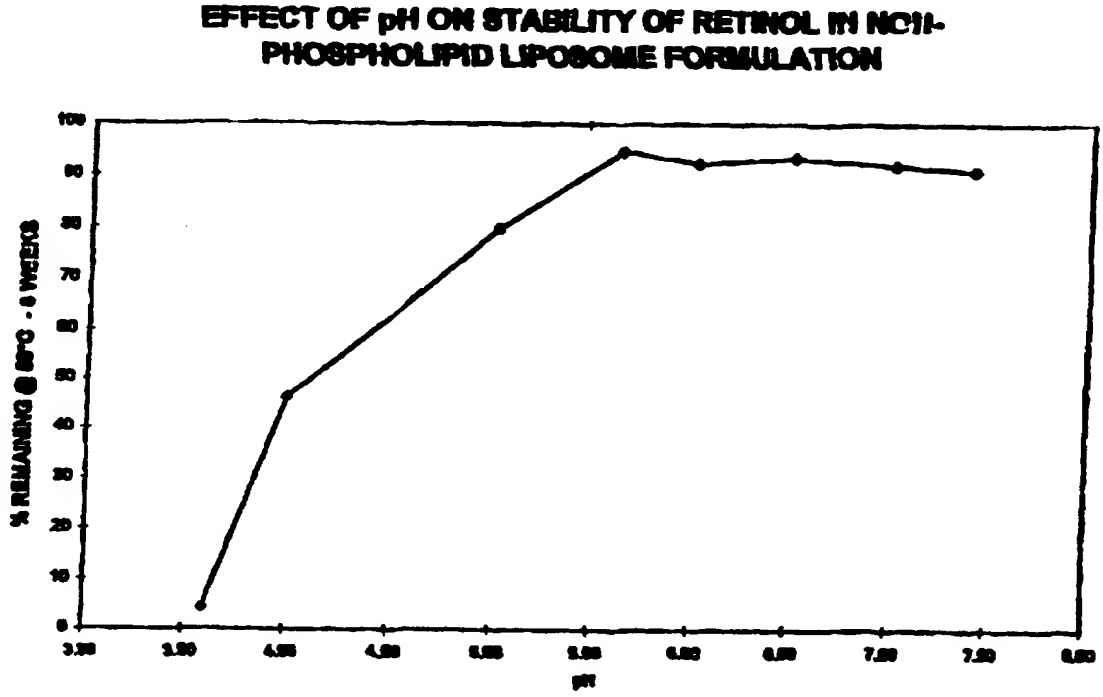

(57) Abstract

This invention relates to a skin care composition containing a retinoid compound as an active ingredient, which is encapsulated in non-phospholipid liposomes and is chemically stable over a long period of time.

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SKIN CARE COMPOSITIONS CONTAINING RETINOIDS AND LIPOSOMES

FIELD OF THE INVENTION

This invention relates to skin care compositions containing retinoids which generally improve the quality of the skin, particularly human facial skin. More particularly, the present invention relates to chemically stable skin care compositions containing a non-phospholipid liposome formulation and certain retinoids.

BACKGROUND OF THE INVENTION

Skin care compositions containing retinoids have become the focus of great interest in recent years. Retinoic acid, also known as Vitamin A acid or tretinoin, is well-known for the treatment of such skin conditions as acne and products containing retinoic acid are commercially available in various forms. Such products, for example, include Retin A® creams, an oil-in-water emulsion of retinoic acid containing an oil-soluble antioxidant, butylated hydroxytoluene (BHT); Retin A® liquid, commercially available from Ortho Pharmaceutical Corporation of Raritan, New Jersey, which is a solution of retinoic acid in a polyethylene glycol/ethanol solvent employing BHT as an antioxidant; and Retin A® gel, which comprises retinoic acid in a gel vehicle comprising ethyl alcohol as the solvent, hydroxypropyl cellulose as the thickener or gelling agent and BHT as an antioxidant.

These retinoic acid containing products have proven stable and capable of providing active ingredients after extended periods of storage. More recently, however, wider use of retinoids has been suggested for treatments other than acne such as, for example, the treatment of skin against photoaging and sun damage. Many individuals who have had a good deal of sun exposure in childhood will show the following gross cutaneous alterations in later adult life: wrinkling, leatheriness, yellowing, looseness, roughness, dryness, mottling (hyperpigmentation) and various premalignant growths (often subclinical). These changes are most prominent in light-skinned persons who burn easily and tan poorly. These cumulative effects of sunlight are often referred to as "photoaging". Although the anatomical degradation of the skin is most advanced in the elderly, the destructive effects of excessive sun exposure are already evident by the second decade. Serious microscopic alterations of the epidermis and dermis occur decades before these become clinically visible. Wrinkling, yellowing, leatheriness and loss of elasticity are very late changes.

U.S. Patent No. 4,603,146 suggests the use of Vitamin A acid in an emollient vehicle as a treatment for ameliorating the effects of photodamage. Further, U.S. Patent No. 4,877,805, suggests that a number of retinoids are useful for restoring and reversing sun damage of human skin.

Certain retinoids such as, for example, retinol (Vitamin A alcohol), retinal (Vitamin A aldehyde) and retinyl esters such as retinyl acetate and retinyl palmitate may be preferable to use in skin care compositions as opposed to retinoic acid. Retinol is an endogenous compound naturally occurring in the human body and essential for good growth,

differentiation of epithelial tissues and reproduction. Retinol is also preferred because it is safer and less irritating to the skin than other retinoids, such as retinoic acid. Additionally, excess retinol is stored in the human body largely in an inactive ester form, e.g. retinyl palmitate and, to some extent, retinyl acetate. The aldehyde, retinal, also a preferred form, is an active metabolite of retinol and is needed for visual function.

Accordingly, attention has turned toward formulating skin care compositions which contain these preferred, naturally occurring retinoids which have similar properties to existing retinoic acid formulations, i.e., providing a composition which is aesthetically pleasing and which can deliver active ingredients after a substantial shelf life.

Typically, existing formulations containing retinoids are oil-in-water emulsions in which the retinoic acid is carried within the oil phase and is protected from oxidation by employing an oil-soluble antioxidant. Oil-in-water emulsions are generally considered preferable to water-in-oil emulsions because they are nonocclusive, non-greasy, compatible with other such emulsion products, easy to remove from the skin and are regarded as more aesthetically pleasing as well as being more economical to manufacture. Generally, the chemical stability of the activ retinoic acid ingredient is quite good in that the oil phase protects th retinoic acid, especially when an oil-soluble antioxidant is present. Thus, for example, the aforementioned Retin A® cream is an oil-in-wat r emulsion containing retinoic acid and BHT, an oil-soluble antioxidant. In U.S. Patent 3,906,108 there is disclosed an oil-in-water emulsion of retinoic acid which may include an oil-soluble antioxidant such as BHT or dl-α-tocopherol and a chelating ag nt .g.ethylen diamin tetraacetic acid (EDTA). In U.S. Patent 4,466,805,

a tanning composition is described which may include,among other ingredients Vitamin A in an oil-in-water emulsion containing Vitamin E and citric acid. In U.S. Patent 4,247,547 still another form of a retinoic acid containing composition, namely a gel, is disclosed and is protected by an antioxidant selected from the group consisting of butylated hydroxytoluene, butylated hydroxyanisole (BHA) , ascorbic acid (Vitamin C) , propyl gallate, and α-tocopherol (Vitamin E).

A number of skin care products have appeared in the marketplace incorporating other retinoids, including, for example, retinol, retinal and retinyl esters such as retinyl acetate and retinyl palmitate. Unsurprisingly, these compositions emulate the formulas of commercial retinoic acid compositions: they are oil-in-water emulsions protected by oil-soluble antioxidants. However, for reasons not yet clearly understood, the retinoids other than retinoic acid in such compositions quickly lose their activity and either oxidize or isomerize to non-efficacious chemical forms with the result that the amount of retinoid actually available to provide the beneficial effects of the product is reduced, in an unacceptably short period of time, to an ineffective quantity and eventually only to trace quantities.

Generally then, products containing retinoids have been limited to oil-in-water emulsions and, with respect to those other than retinoic acid, have suffered from chemical instability. In a few instances, however, products and/or suggestions for products have been made wherein retinoids such as retinol, retinyl acetate and retinyl palmitate are formulated in water-in-oil emulsions.

Thus, for example, in U.S. Patent 4,826,828 describes a stable composition comprising retinol, retinyl acetate and retinyl palmitate may consist of retinol in a water-in-oil emulsion wherein the emulsion further include two oil-soluble antioxidants, BHT and BHA.

Further, Avon Products, Inc., the assignee of U.S. 4,826,828, sells two skin care products called Bioadvance and Bioadvance 2000. Each of thes products is supplied in two bottles, portions of which are mixed together just prior to use. The first bottle contains what is called a "skin lotion", while the second bottle contains what is called a "fortifier". The "skin lotion" is a water-in-oil emulsion having a number of ingredients which include water, emulsifiers, silicone and vegetable oils, preservatives, emollients and butylated hydroxytoluene (BHT) The "fortifier" is a non-aqueous solution which contains a number of ingredients including cyclomethicone (a silicone oil), denatured ethanol, an emulsifier (Polysorbate 20), retinol, retinyl acetate, retinyl palmitate, BHT and BHA. When a specified portion of the "fortifier" is added to a specified porti n of the "skin lotion" and mixed, there results a water-in-oil emulsion which comprises retinol, retinyl acetate, retinyl palmitate, BHT and BHA, the latter being oil-soluble antioxidants. The outer package in which Bioadvance is supplied carries a statement which says "Because BIOADVANCE begins to lose effectiveness after one month, for maximum benefits, use a fresh supply each month". It would appear from this statement that the chemical stability of the retinoids in the mixture of the "skin lotion" and the "fortifier" is quite limited. The fact that in both the BIOADVANCE and BIOADVANCE 2000 products the "fortifier" ingredients must be mixed with the "skin lotion" ingredients immediately prior to use indicates that the resulting water-in-oil emulsion which is applied to the skin also has

limited chemical stability of one or more of the above-mentioned retinol, retinyl acetate and retinyl palmitate.

Further still, U.S. 4,720,353 to Bell describes water-in-oil emulsion carriers for various medicaments and drugs intended for topical application to the skin. Water soluble, miscible or dispersible drugs may be incorporated into the aqueous phase of the emulsion. Oil-soluble, miscible or dispersible drugs may be incorporated into the oil phase. Drugs which may be incorporated into the emulsion include derivatives of retinoic acid. Ingredients which may optionally be added to the emulsion include a preservative such as methyl paraben, propyl paraben or imidazolidinyl urea or an antioxidant such as butylated hydroxyanisole and a water or oil soluble vitamin such as vitamin C, tocopherol linoleate and the like.

Still further, EP 0 343 444 A2 to Siemer et al discloses cosmetic preparations based on retinyl palmitate. Example 3 discloses a night cream in the form of an water-in-oil type emulsion comprising retinyl palmitate and butylated hydroxyanisole (BHA). Example 4 discloses a water-in-oil emulsion comprising retinyl acetate and a-Tocopherol (Vitamin E).

Still further, EP 0 330 496 A2 to Batt is directed to skin treatment compositions comprising a topically acceptable base and an effective amount of at least one ester of retinol, said compositions being useful in the treatment of photoaged skin. Example 6 discloses a water-in- il emulsion comprising Vitamin A propionate and BHT, an oil soluble antioxidant.

Unfortunately, none of these prior attempts to emulate the stability of th retinoic acid containing compositions have been successful for retinoids

other than retinoic acid and in each case result in substantial and unacceptable chemical instability of the retinol, retinal or retinoic esters employed therein. Accordingly, there is a need for a composition in which such non-retinoic acid retinoids may be provided in a chemically stable form.

Jonas C.T. Wang, et.al in pending application USSN 719,764 filled November 15, 1993 disclose the stabilization of retinol in a water-in-oil emulsion, in which retinol was dispersed and protected in oil phas . However, oil-in-water emulsions are much more preferred than water-in-oil emulsions based on the cosmetic performance. This is due to the fact that oil-in-water emulsions, in general, are less occlusive, less greasy, compatible with make-up and easy to be removed from the skin leading t a more aesthetically pleasing feel. In addition, oil-in-water formulations are less costly considering the ingredient composition and the manufacturing process.

It is therefore desirable to develop efficacious and also cosmetically elegant skin care products containing retinoids including retinoic acid, retinal, retinol, and retinyl esters to enhance the broad usage of retinol for skin treatment.

It is another object of this invention to provide skin care compositions containing retinoids which have acceptable shelf-lives.

It is yet another object of this invention to provide a skin care composition containing retinoids, which permits the controlled release of active ingredients to the skin over time.

Another object of this invention is to provide a method for making a stable skin care composition containing retinoids, which retains its activity over a long time period.

It is yet another object of this invention to provide skin care compositions which are relatively non-irritating and yet efficacious in delivering active ingredient to the skin.

Other objects of this invention will become clear throughout the description provided, below.

BRIEF DESCRIPTION OF THE DRAWINGS

Figure 1 is a graph depicting the effect of pH on stability of retinol in non-phosphoipid liposome formulations.

Figure 2 is a graph depicting the amount of retinol released from th formulation of Example 8C compared with that of a water-in- il formulation.

Figure 3 is a graph depicting the amount of active ingredient which permeates the epidermis and dermis from the formulations of Examples 8C and 6 in comparison with that of a water-in-oil formulation.

Figure 4 is a graph depicting the sensory perceptions of certain formulations of this invention in comparison with other skin care compositions.

SUMMARY OF THE INVENTION

In accordance with the present invention, it has now been discovered that, unexpectedly, certain retinoids may be successfully stabilized against chemical degradation by incorporating them into non-phospholipid liposomes using a specifically defined stabilizing system and process. The retinoids which can be stabilized against chemical degradation in accordance with the principles of the present invention include retinol (Vitamin A alcohol) , retinal (Vitamin A aldehyde), retinyl acetate, retinyl palmitate and mixtures thereof.

As used herein, the "chemical stability" or "stability" of a retinoid is defined in terms of the percentage of the specified retinoid which is retained in its original chemical form after the composition has been stor d for a specified period of time at a specified temperature. Thus, if th original concentration of all-trans retinol in an absolute ethanol solution were 0.20% by weight and, after two (2) weeks storage at room temperature (21°C ± 1°C) , the concentration of all-trans retinol were 0.18% by weight, then the original solution of all-trans retinol in abs lut ethanol would be characterized as having a chemical stability of retin l of 90% after two weeks storage at room temperature. In the same fashi n, if an non-phospholipid liposome formulation comprising all-trans retinol had an initial concentration of 0.30% by weight and after storage for 13 we ks at 50°C had a concentration of all trans-retinol of 0.24% by weight, then the original emulsion would be characterized as having a chemical stability of retinol of 80% after 13 weeks storage at 50°C.

For the specific retinoids which are the subject of this invention the n n-phospholipid liposome form, in c mbination with the sel ction of a stability

system from those described her in, will produce compositions having a chemical stability of 80% after 13 weeks' storage at 50°C. The present invention also provides a system for stabilizing retinoids, unexpectedly, without the presence of a water-soluble antioxidant.

Accordingly there is provided, in accordance with the teachings of the present invention, a skin care composition comprising a non-phospholipid liposome and a retinoid selected from the group consisting of retinol, retinal, retinyl acetate, retinyl palmitate and mixtures thereof, said composition further comprising a stabilizing system selected from the group consisting of:

a) an oil-soluble antioxidant; and

b) a chelating agent and at least one oil-soluble antioxidant;

wherein said composition has a pH from at least about 5 to about 10, said composition retaining at least about 80% of said retinoids after 13 weeks storage at 50°C.

It was also discovered unexpectedly that the compositions of this invention can be endowed with material changes resulting in a controlled-release f active agent from the liposome carrier. The compositions of this inventi n may also be moderated in order to enhance or diminish penetration of the active ingredient into the skin.

Surprisingly, compositions of the present invention containing a relatively high level of surfactants (e.g., >8%) exhibit irritation at the same level as that experienced by individuals exposed to a water-in-oil cream containing 2% surfactant.

DETAILED DESCRIPTION OF THE INVENTION

As described above, the composition of the invention is in the form of a particular type of liposome, namely, a non-phospholipid liposome.

Most commercial skin care compositions such as the ones containing retinoic acid are oil-in-water emulsion systems. In such oil-in-water emulsion systems, certain retinoid compounds, in particular, retinol, retinal, and the retinyl esters tend to be chemically unstable, i.e. they degrade, either by way of oxidation or isomerization, and are, therefore, not available to perform in their desired manner. While this is not clearly understood, it is believed that this degradation occurs as a result of the rapid diffusion of oxygen through the external water phase to the internal oil phase containing the retinoid. The oxygen is readily available to degrade the retinoid. Because the diffusion of oxygen is greater in a water phas than an oil phase, an oil-in-water system is more prone to such degradation.

The compositions of the present invention overcome these difficulties and instead, provide a non-phospholipid liposome composition containing at least one retinoid compound wherein both the physical stability of the liposome and the chemical stability of the active ingredients are maintained at high levels.

Liposomes are spherical, self-closed structures composed of curved lipid bilayers which entrap part of the solvent, in which they freely float, into their interior. They may consist of one or several concentric membranes. Liposomes are made predominantly from amphiphiles, a special class f surface active molecules, which are characterized by having a hydrophilic

and a hydrophobic group on the same molecule. These molecules are not soluble in water; and, rather than forming solutions, they form colloidal dispersions.

Until recently, liposome technology has been concerned mostly with vesicles composed of phospholipid. Phospholipids are labile and expensive to purify or synthesize. In addition, manufacture of phospholipid liposome is difficult and costly to scale up. For these reasons there has been increasing interest in non-phospholipid liposomes. Certain double-chain synthetic surfactants with non-ionic polar heads and single-chain surfactants in mixture with cholesterol can form non-ionic liposome. They have increased chemical stability over natural phospholipid and are easy to make in large, commercial quantities.

Because of their solubility properties the structure of these aggregates involves the ordering of lipid molecules: the hydrophilic part tends to be in contact with water while the hydrophobic hydrocarbon chains prefer to b hidden from water in the interior of the structures. One of the most frequently encountered aggregate structures is a lipid bilayer. On the surface of either side are polar heads which shield non-polar tails in the interior of the lamella from water. At higher lipid concentrations these bilayers from lamellar crystalline phases where two-dimensional planar lipid bilayers alternate with water layers. Upon dilution, these lipid bilayers f rm liposomes. These liposomes can entrap hydrophilic materials in the aqueous compartments and lipophilic materials in the bilayers. Molecules that are entrapped in the bilayers are sometimes referred to as "cargo molecules". Lipophilic entrapment is severely limited by the ability of the bilayer to entrap the cargo molecule.

Liposomes can be large or small and may be composed of from one to several hundred concentric bilayers. With respect to the size and the number of lamellae, they are distinguished as large multilamellar vesicles (MLV's) and large and small unilamellar vesicles (LUV's and SUV's respectively). Most of the research to date have centered on above mentioned type of vesicles.

Recently, Donald F.H Wallach (U.S. Patent number 4,911,928) described another type of lipid vesicles, the paucilamellar lipid vesicles (PLV). The invention describes the PLV's consisting of 2 to 8 peripheral bilayer surrounding a large unstructured central cavity which can be filled wholly or in part with an apolar oil or wax. The multiple lipid bilayer and an apolar core of the PLV'S provide PLV'S with the capacity to transport a greater amount of lipophilic materials.

Still further, U.S. 5,147,723 to Donald F. H. Wallach describes the non-phospholipid surfactants which can form paucilamellar lipid vesicles. The surfactant can be selected from a group consisting of polyoxyethyl ne fatty esters having the formula R_1-$COO(C_2H_4O)_nH$ where R_1 is a radical f lauric, myristic, cetyl, stearic or oleic acid and n is an integer from 2 to 10; polyoxyethylene fatty acid ethers, having the formula R_2-$CO(C_2H_4O)_mH$ where $R_2$is a radical of lauric, myristic, or cetyl acids, single or double unstaurated octadecyl acids, or double unsaturated eicodienic acids and m is an integer from 2 to 4; polyoxyethylene (20) sorbitan mono- or trioleate; and polyoxyethylene glyceryl monostearate with from 1 to 10 polyoxyethylene groups.

All these structures have many interesting physical and chemical properties, such as osmotic activity, permeability of their membranes t

different solutes, solubilizing power, interaction with various hydrophobic and hydrophilic solutes, or aggregation behavior which can depend on temperature, chemical composition and surface characteristics of the membrane, and presence of various agents.

The oil-soluble antioxidants which are useful in the compositions of the present invention include butylated hydroxytoluene (BHT), ascorbyl palmitate, butylated hydroxyanisole (BHA), a-tocopherol, phenyl-a-naphthylamine, hydroquinone, propyl gallate, nordihydroguiaretic acid, and mixtures thereof as well as any other known oil-soluble antioxidant compatible with the other components of the compositions.

The oil-soluble antioxidants useful in the compositions of this invention should be utilized in a stabilizing effective amount and may range in total from about 0.001 to about 5% based on the weight of the total composition, preferably from about 0.01 to about 1%. The amount of antioxidants utilized in the compositions of the present invention is dependent in part on the specific antioxidants selected, th amount of and specific retinoid being protected and the processing conditions. For example, a retinol formulation should include BHT in th amount of from about 0.01% to about 1% by weight. A retinal formulation should include BHT in the amount of from about 0.01% to about 1% by weight.

In certain aspects of this invention, the compositions may include a chelating agent during the scale-up process to minimize metal ion contamination. The retinoid compounds of this invention are sensitive to metal ions and in particular to bi- and tri-valent cations and in certain instances, appear degrade rapidly in th ir pres nce. The

chelating agent forms a complex with the metal ions thereby inactivating them and preventing them from affecting the retinoid compounds. Chelating agents which are useful in the compositions of the present invention include ethylenediamine tetraacetic acid (EDTA) and derivatives and salts thereof, dihydroxyethyl glycine, citric acid, tartaric acid, and mixtures thereof. The chelating agents should be utilized in a stabilizing effective amount and may range from about 0.01 to about 2% based on the weight of the total composition, preferably from about 0.05 to about 1%.

The retinoid compounds which are useful in the compositions of the present invention consist of Vitamin A alcohol (retinol) , Vitamin A aldehyde (retinal) and Vitamin A esters (retinyl acetate and retinyl palmitate). These retinoids are utilized in the compositions of the present invention in a therapeutically effective amount that may range from about 0.001 to about 5% by weight of the total compositions, preferably from about 0.001 to about 1%.

The skin care compositions of the present invention comprising a non-phospholipid can be in the format of cream or lotion formulations, as desired, by varying the relative quantities of the lipid and water phases f the emulsion. The pH of the compositions should be in the range of from at least about 5 to about 9, and preferably from about 5 to about 7.

Any of the many formulations or compositions of the cream or lotion type currently utilized in skin care preparations can be employed provided that it is in a non-phospholipid and is chemically compatible with the retinoid compounds. The ratio of the oil phase of the non-phospholipid liposome t the water phase can be from ab ut 5:95 to about 40:60. Th actual rati

of the two phases will depend on the desired final product.

The advantages of the invention and specific embodiments of the skin care compositions prepared in accordance with the present invention, as well as comparisons with compositions outside the scope of the claimed invention are illustrated by the following examples. It will be understood, however, that the invention is not confined to the specific limitations set forth in the individual examples, but rather to the scope of the appended claims.

COMPARISON EXAMPLE 1

Three oil-in-water emulsions of retinol (Vitamin A alcohol) were prepared having the % w/w compositions set forth in Table 1. In Table 1, the appellation "o/w" indicates an oil-in-water composition. These emulsions were prepared according to the following procedure. The ingredients shown under the heading "Aqueous Phase Ingredients" were added to a first glass container equipped with a stainless steel stirrer and heated with stirring to 75°C-85°C under an argon gas blanket. The ingredients shown under the heading "Oil Phase Ingredients" were added to a second glass container equipped with a stainless steel stirrer and heated with stirring to about from 85°C to 90°C under an argon gas blanket. The ingredients shown under the heading "Retinoid Mixture" were added to a third glass container equipped with a stainless steel stirrer and stirred at room temperature under a blanket of argon gas. Stirring was continued in all instances until uniformity was achieved. The Aqueous Phase Ingredients at 75°C-85°C were then added to the Oil Phase Ingredients. During this addition step, the Oil Phase Ingredients were maintained at 85°C-90°C with stirring under an argon gas blanket. The mixture of the Aqueous

Phase Ingredients and Oil Phase Ingredients was stirred, at a temperature in the range of 90°C and under the argon gas blanket until a uniform oil-in-water emulsion was obtained. After the resulting emulsion was cooled to about 50°C-53°C, the Retinoid Mixture was added with stirring. The emulsion was blanketed under argon gas and the temperature was maintained at about 50°C-53°C during the addition of the Retin id Mixture. After the addition of the Retinoid Mixture was completed, the emulsion was gradually cooled, with stirring and under an argon blanket, to room temperature (approximately 21°C). The finished emulsion was then transferred under argon gas blanketing to blind end aluminum tubes (2 ounce size) which were promptly crimped and tightly capped. The closed tubes were then set aside for determination of retinol stability after storage for various time periods at various temperatures. Retinol degrades under the influence of UV light. Accordingly, care must be taken at all stages of the emulsion preparation process to protect the retinol from exposure to UV light. This can be accomplished by turning out the lights in the processing area or by conducting the various handling and processing steps under yellow light.

TABLE 1

Sample Designation	A	B	C
Water, q.s 100%	----	----	----
Propylene Glycol	4.00	4.00	4.00
Carbomer 934	0.50	0.50	0.50

Oil Phase Ingredients

Mixture A	8.75	8.75	8.75
Polysorbate 61 (Tween 61)	1.20	1.20	1.25
Dimethicone	1.00	1.00	1.00
Sorbitan Stearate	0.80	0.80	0.80

Retinoid Mixture

Ascorbic Acid	0.00	0.00	0.10
EDTA	0.00	0.10	0.10
Benzyl Alcohol	0.30	0.30	0.30
50% NaOH, q.s. pH 4.7	----	---	---
Methyl Paraben	0.15	0.15	0.15
Propyl Paraben	0.10	0.10	0.10
Butyl Paraben	0.05	0.05	0.05
BHT	0.02	0.02	0.02
Fragrance	0.25	0.25	0.25
Retinol (all trans), USP	1.00	0.86	0.86
Emulsion Type	o/w	o/w	o/w

In the above Table 1, the ingredient in the Oil Phase Ingredients designated as Mixture A consisted of 1.50 g myristyl myristate; 1.25 g oleic acid (Emersol 228); 1.25g glyceryl stearate (Emerest 2400); 1.25 g stearic acid (Emersol 132); 1.00 g isopropyl palmitate; 1.00 stearoxytrimethylsilane (Dow Corning 580 Wax); 0.50 synthetic beeswax; 0.50 g stearyl alcohol; and 0.50 g cetyl alcohol. Mixture A was prepared by mixing the indicated ingredients in a glass container, stirring with heat until all ingredients were

liquefied and uniformly mixed; pouring the liquefied mixture into shallow containers; and allowing the mixture to cool to ambient temperature.

Concentrations of all-trans retinol in oil-in-water samples A, B and C in Table 1 were determined after storage for various time periods at various temperatures. Concentrations of retinol and other retinoids such as retinal (vitamin A aldehyde), retinyl acetate and retinyl palmitate can be determined by any suitable analytical procedure. As reported herein, we determined retinoid concentrations by a stability indicating high performance liquid chromatography (HPLC) procedure in which the chromatograph was equipped with a reversed phase 5 micron C-8 column (25 cm in length x 4.6 mm in diameter) and a UV detector at 340nm. Th sample to be analyzed was diluted with a solution of 50% by weight methanol and 50% by weight ethyl acetate to a concentration of 18 micrograms/ml and the retinoid was detected at 340nm. The gradient mobile phase consisted of an organic portion composed of 5 percent tetrahydrofuran in acetonitrile and an aqueous portion consisting of 0.05N ammonium acetate. The solvent program has an initial composition of 70% organic/30% aqueous which increases linearly to 80% organic/20% aqueous at 13 minutes, then again increases linearly to 100% organic at 15 minutes, where it stays until 19 minutes. After injecting 15 microliters of sample solution into the chromatograph, the analytical conditions were run at a flow rate of 2 ml/min and thermostatically regulated at 40°C. The retention time of retinol (Vitamin A alcoh l) is about 6.4 minutes. The retention times of retinal (Vitamin A aldehyde), retinyl acetate, and retinyl palmitate are about 7.5 mins., 10.1 mins. and 18.7 mins. , respectively. The HPLC results wer

found to be reproducible to better than a 3% range of standard deviation.

The results were as follows:

For Sample A: After twenty-six (26) weeks aging at room temperature (21°C ± 10°C), only 39% of the original amount of all-trans retinol was found in the emulsion. After twenty-six (26) weeks aging at 40°C, only three percent (3%) of the original amount of all-trans retinol was found in the emulsion.It is concluded that an oil-in-water emulsion comprising retinol and butylated hydroxytoluene (BHT), an oil-soluble antioxidant, does not have acceptable retinol chemical stability.

For Sample B: After thirteen (13) weeks aging at room temperature, 87% of the original amount of all-trans retinol was found in the emulsion. After thirteen (13) weeks aging at 40°C, just four percent (4%) of the original amount of all-trans retinol was found in the emulsion. After thirteen (13) weeks aging at 50°C, no amount of all-trans-retinoic acid was detected in Sample B. After twenty-six (26) weeks aging at room temperature, fifty-seven percent (57.%) of the original amount of all-trans retinol was found in the emulsi n. It is concluded that chemical stability of all-trans retinol in an oil-in-water

emulsion comprising all-trans retinol, BHT and disodium EDTA (a chelating agent) does not have acceptable chemical stability.

For Sample C: After thirteen (13) weeks aging at room temperature, sixty percent (60%) of the initial amount of all-trans retinol was found in the emulsion, while after thirteen (13) weeks aging at 40°C, twenty-thr e percent (23%) all-trans retinol was detected. No amount of all trans-retinol was detected after Sample C was stored for thirteen (13) weeks at 50°C.

After twenty-six (26) weeks aging at room temperature, forty-two percent (42%) of the initial amount of all-trans retinol was found in Sample C; aft r fifty-two (52) weeks aging at room temperature, thirty-one percent (31%) of the initial concentration of all-trans retinol remained in Sample C.

From the foregoing aging results, it is concluded that the chemical stability of all-trans retinol in an oil-in-water emulsion comprising all-trans retinol, an oil-soluble antioxidant (BHT) , a water-soluble antioxidant (ascorbic acid) and a chelating agent (ethylenediaminetetraacetic acid) is chemically unacceptable.

COMPARISON EXAMPLE 2

A phospholipid liposomal formulation of retinol (Vitamin A alcohol) was prepared having the % w/w composition set forth in Table 2 at CILAG AG. After four weeks aging at 50°C, only 64.87% of the original amount of retinol was found in the formulation which does not meet the stability criteria.

Table 2:

Ingredients	% w/w
Water purified	81.44
Lecithin purified soya	7.50
Cholesterol	1.00
Ethanol	8.00
BHT	0.01
Methylparaben	0.14
Propylparaben	0.01
Edetate Disodium Dihydrate	0.10
Citric Acid Monohydrate	0.23
Sodium Hydroxide	0.44
Carbomer 934P	0.80
Retinol (45%)	0.33

COMPARISON EXAMPLE 3

A phospholipid liposomal formulation of retinol (Vitamin A alcohol) was prepared by BioZone according to U.S Patents Nos. 4,485,054 and 4,761,288. After four weeks aging at 50°C, only 64.61% of the original amount of

retinol was found in the formulation which does not meet the stability criteria.

COMPARISON EXAMPLE 4

A non-phospholipid liposomal formulation of retinol (Vitamin A alcohol) was prepared by Micro Vesicular Systems, Inc. of New Jersey according to U.S. Patent No. 4,911,928. After 12 weeks aging at 50°C, 40°C and room temperature only 58.1% , 79.4% and 89.3% respectively of the original amount of retinol was found in the formulation which does not meet the stability criteria.

The results clearly demonstrated that retinol was more stable in b th phospholipid and non-phospholipid liposome type formulation than in th oil-in-water emulsion. Although retinol was partially stabilized by formulation type change from o/w to non-phospholipid liposome, the shelf-life at ambient temperature was only 12 weeks, that is still chemically unacceptable.

EXAMPLE 5 and 6:

Retinol was encapsulated in the non-phospholipid liposome formulation with the following composition in accordance with the procedure set forth below. The pH of the final formulation was about 5.6.

	Example 5	Example 6
Oil Phase:	%W/W	%W/W
Caprylic Capric Triglyceride	10.00%	10.00%
Cholesterol	5.56%	6.80%
Glyceryl Distearate	4.33%	5.30%
Stearyl Alcohol	3.90%	4.75%
Steareth-10	3.28%	4.00%
Glyceryl Monostearate	2.08%	2.55%
Polysorbate 80	1.00%	1.05%
Tocopherol Acetate	0.15%	0.34%
Butylated Hydroxy Toluene	0.05%	0.05%
Water Phase:		
Deionized Water	68.14%	63.90%
Citric Acid	0.13%	0.12%
Sodium Hydroxide	0.03%	0.07%
Methyl Paraben	0.20%	0.20%
Propyl Paraben	0.03%	0.03%
Active Ingredient:		
Retinol (45% W/W)	1.12%	0.34%

Under a yellow light and inside an argon blanket, which served to diminish the amount of oxygen in the formulation, the oil phase components were mixed together and heated to a temperature of about 85°C. The water

phase components were then mixed together and heated to a temperature of about 85°C and then cooled to 60°C before phasing. the water phase was then purged with argon to remove oxygen. A Novosome® liposome maker, commercially available from Micro Vesicular Systems of New Jersey and described in U.S Patent Number 4,895,452) was equilibrated to a temperature of about 60°C by pumping the water phase through the equipment. 1.13% of retinol (45% active was added to the oil phas . Both the water phase and the oil phase were pumped through th Novosome® maker and the product was collected in a stainless steel jacketed kettle (manufactured by fryma) which had been blanketed with argon. The kettle was equipped with a scraper-stirrer, toothed colloid mill, dissolver and vacuum deaeration system. The product was vacuum d until the pressure in the kettle dropped to 0.8 mBar. The products were dispensed into proper packages under the argon blanket. Proper packages may be selected from aluminum tubes, cans, pumps and/or sprays.

The stability results shown in Table 3 and 4 clearly illustrate that retinol is more stable in example 5 and 6 than in example 4 and also meet the stability criteria 80% remaining at 50°C after 13 weeks of storage. Th re is no significant difference on the stability of retinol as its concentration is changed from 0.153% to 0.504%.

Table 3. Retinol Stabilities in Example 5 at Various Temperatures.

	% Retinol	% Initial	pH
Initial	0.5059	100	5.53
3 weeks 50°C	0.4498	88.91	5.32
8 weeks			
40°C	0.4704	92.98	5.36
50°C	0.4636	91.64	5.32
13 weeks			
30°C	0.4884	97.0	5.37
40°C	0.4566	90.69	5.33
50°C	0.4355	86.5	5.22
26 weeks			
30°C	0.4754	93.97	5.43
40°C	0.4454	88.04	5.28

Tabl 4. Retinol Stabilities in Example 6 at Various Temperatures.

	% Retinol	% Initial	pH
Initial	0.153	100	5.64
4 weeks			
40°C	0.143	93.46	5.65
50°C	0.142	92.81	5.61
8 weeks			
40°C	0.1375	89.87	5.60
50°C	0.1355	88.56	5.56
13 weeks			
40°C	0.1335	87.25	5.55
50°C	0.1275	83.33	5.55
20 weeks			
30°C	0.1375	89.87	5.69
40°C	0.1295	84.64	5.62
50°C	0.1220	79.74	5.56

EXAMPLE 7:

To further improve the formulations of this invention, a formulation with a water soluble antioxidant ascorbic acid and a chelating agent disodium EDTA was prepared in dark room without an Argon blanket set forth below..

The data summarized in Table 5 suggest that the stability of retinol in Example 7 was comparable to Example 5 which was prepared without ascorbic acid and disodium EDTA but under yellow light and Argon blanket. The results also suggest that the addition of ascorbic acid/disodium EDTA might enhance the chemical stability of retinol in Novasome® liposomes without the need for using an argon blanket. Thus, water-soluble antioxidants may also be utilized in the compositions of this invention such as ascorbic acid, sodium sulfite, sodium metabisulfite, sodium bisulfite, sodium thiosulfite, sodium formaldehyde sulfoxylate, isoascorbic acid, thioglycerol, thiosorbitol, thiourea, thioglycolic acid, cysteine hydrochloride, 1-4-diazobicyclo-(2,2,2)octane and mixtures thereof.

		% W/W
	Glyceral Distearate	2.80%
	Cholesterol	1.00%
	POE-10 Stearyl Alcohol	1.40%
5	Stearyl Alcohol and Ceteareth-20	1.50%
	Cetearyl Alcohol and Ceteareth-20	1.00%
	Cetyl Acetate and Acetylated Lanolin Alcohol	1.00%
	Dow Corning 344 Fluid Silicone Oil	5.00%
	Tocopherol	0.15%
10	Butylated Hydroxy Toluene	0.05%
	Glycerine	10.00%
	Methyl Paraben	0.20%
	Propyl Paraben	0.03%
	Sodium Chloride	0.10%
15	Polysorbate 80	0.75%
	Ascorbic Acid	0.10%
	Disodium EDTA	0.10%
	Butylene Glycol	10.00%
	C12-15 Alkyl Benzoate	6.70%
20	Retinol (45% W/W)	1.12%
	10 mM Citric Acid Buffer	57.00%

Table 5. Retinol Stability in Example 7.

	%RETINOL	%INITIAL	pH
INITIAL	0.491	100	5.56
50°C			
3 weeks	0.459	93.48	5.56
7 weeks	0.449	91.45	5.47
12 weeks	0.407	82.89	5.60

EXAMPLE 8:

To improve the cosmetic elegance of the retinol formula, the non-phospholipid liposomal formulation of retinol (Example 8A) was physically mixed with various proportions of 30% w/w cyclomethicone loaded non-phospholipid liposome (Example 8B). The stability results are summarized in Tables 6 through 8.

Example 8A

	% W/W
Water	54.95%
Caprylic Capric Triglyceride	6.00%
Glycerin 96%	10.00%
Butylene Glycol	10.00%
Cholesterol	3.95%
Glyceryl Distearate	3.15%
Stearyl Alcohol	2.85%
Steareth-10	2.50%
Tocopherol Acetate	2.00%
Glyceryl Monostearate	1.58%
Polysorbate 80	1.00%
Retinol (45% W/W)	0.75%
Citric Acid	0.50%
Sodium Hydroxide	0.25%
Methyl Paraben	0.20%
Disodium EDTA	0.10%
Butylated Hydroxy Toluene	0.10%
Ascorbic Acid	0.10%
Propyl Paraben	0.03%

Example 8B (30% w/w Cyclomethicone Loaded Non-phospholipid Liposome)

	% W/W
Water	40.10%
Cyclomethicone	30.00%
Glyceryl Distearate	7.95%
Glycerin 96%	7.00%
1,3-Butylene Glycol	7.00%
Steareth-10	3.98%
Cholesterol	1.97%
Sodium Citrate	0.95%
Polysorbate 80	0.52%
Citric Acid	0.16%
Methyl Paraben	0.14%
Tocopherol Acetate	0.11%
Ascorbic Acid	0.07%
Disodium EDTA	0.07%
Propyl Paraben	0.02%

Table 6. Example 8C (50% Example 8A & 50% Example 8B)

	% Retinol	% Initial	pH
Initial	0.1735	100	5.56
4 weeks			5.54
40°C	0.1705	98.27	5.54
50°C	0.1690	97.41	
8 weeks			
40°C	0.1690	97.41	5.53
50°C	0.1670	96.25	5.56
13 weeks			
30°C	0.1660	95.68	5.52
40°C	0.1650	95.10	5.58
50°C	0.1580	91.07	5.57
20 weeks			
30°C	0.1715	98.84	5.61
40°C	0.1655	95.39	5.60
50°C	0.1550	89.34	5.60

Table 7. Example 8D (60 % Example 8A and 40% Example 8B)

	% Retinol	% Initial	pH
Initial	0.1900	100	5.62
4 weeks			
40°C	0.1869	98.37	5.57
50°C	0.1831	96.37	5.57
8 weeks			
30°C	0.1896	99.77	5.57
40°C	0.1858	97.78	5.64
50°C	0.1816	95.59	5.62
13 weeks			
30°C	0.1867	98.26	5.65
40°C	0.1809	95.21	5.64
50°C	0.1750	92.11	5.64

Table 8. Example 8E (70% Example 8A and 30% Example 8B)

	% Retinol	% Initial	pH
Initial	0.2235	100	5.64
4 weeks			
40°C	0.2201	98.50	5.64
50°C	0.2161	96.70	5.62
8 weeks			
30°C	0.2213	99.04	5.62
40°C	0.2181	97.58	5.67
50°C	0.2138	95.67	5.66
13 weeks			
30°C	0.2205	98.66	5.66
40°C	0.2146	96.02	5.66
50°C	0.2075	92.84	5.67

The data suggest that there are no significant changes in stability of a non-phospholipid liposomal retinol formulation when it is mixed with 30-50% of 30% cyclomethicone loaded non-phospholipid liposome formulation to render cosmetic elegance to the primary formula. This was of great significance because the elegance characteristic is of profound importance for customer compliance.

Example 9:

The Effect of pH on Stability of Retinol in a Non-Phospholipid Liposome Formulation.

To define the pH range most useful for retinol-containing compositions of this invention, the pH of Example 8D was adjusted to pH's ranging from 3.6 to 7.4 with dilute hydrochloric acid or dilute sodium hydroxide. The samples were stored at different temperatures (4°C, 30°C, 40°C and 50°C). Samples were taken periodically for both physical and chemical evaluation. The results in Figure 1 clearly showed that optimal pH range for retinol cream at 50°C was above 5 .

EXAMPLE 9:

In-vitro Bioavailability of Liposome Formulations

Skin bioavailability, which is defined by the availability of drug released from the formulation as well as the extent of skin penetration after application, usually serves as a good indicator for drug efficacy. The *in-vitro* bioavailability of retinol was determined by standard in-vitro release and skin penetration tests using FRANZ diffusion cells. For the release study, a weighed amount of cream was applied on a synthetic membrane mounted on each of the FRANZ diffusion cells. The synthetic membrane functioned as a cream supporter and did not cause significant resistance to the drug release. Samples were taken from the receptor chamber at predetermined intervals. The amount of retinol released from the formulation to the receptor solution was determined by High Pressure Liquid Chromatography

(HPLC). The results in Figure 2 clearly showed that the release of retinol from non-phospholipid liposome Example 8C is much faster than that from RoC s.a (water-in-oil, 0.15% retinol) formulation, a stable retinol water-in-oil cream produced according to Wang, et.al. pending patent on the market. At the end of 7 hours, approximately 10% and 5% of retinol were released from non-phospholipid liposome and RoC s.a respectively.

The ***in-vitro*** skin penetration study was conducted using a similar protocol as the release study except that human cadaver skin was used instead of a synthetic membrane. At the end of 48 hrs of experiment, the skin surface was thoroughly cleaned and the amount of retinol penetrated was analyzed by HPLC. It was found that non-phospholipid liposome formulations can be engineered to provide a wide range of bioavailability. For example, Example 8C (which is a 50:50 mixture of 0.34% retinol loaded non-phospholipid liposome and 30% cyclomethicone loaded non-phospholipid) yielded much higher retinol skin penetration compared to the RoC s.a product. On the other hand, Example 6 (0.15% retinol loaded non-phospholipid) provided similar skin penetration to RoC s.a product (Figure 3).

EXAMPLE 10:

Dermal Irritation Test:

Retinol-containing non-phospholipid liposome formulations were evaluated for dermal irritation and were also compared with a water-in-oil retinol formulation.

Scope and Procedure

The modified Draize Rabbit Primary Dermal Irritation Test is a procedure for predicting the ability of test articles to elicit inflammatory responses upon prolonged occluded contact with intact and intentionally-abraded New Zealand white rabbit skin. Following a timed exposure period, the test articles are removed and the application sites were evaluated. From this data, a Primary Dermal Irritation (PDI) Index is calculated for each test article and a classification is assigned.

The test article was applied with 0.25-0.30g to 25mm Hilltop Chambers containing non-woven Webril pads. The chambers were then applied to the appropriate test sites and held in place with strips of Dermicel tape. The trunk of the animals were wrapped to occlude the sites and to keep the test articles in place. After the 4 hours of exposure, the test articles were removed and readings were taken after one hour in order to allow the skin to equilibrate. After the equilibration period, the sites were examined and then again reexamined after 72 hours of application for signs of dermal irritation and were graded using a scale as follows:

PDI Index	Classification
0.0	Non-irritant
0.1 - 2.0	Mild Irritant
2.1 - 5.0	Moderate Irritant
5.1 - 8.0	Severe Irritant

Table 9:

		PDI	Classification
Study I	Formulation 6(0.15% Retinol)	0.9	Mild irritant
	Placebo (negative control)	0.7	Mild Irritant
	w/o-I (0.15% Retinol	1.7	Mild Irritant
	Placebo (negative control)	0.5	Mild Irritant
Study II	Formulation 8C (0.15% Retinol)	3.0	Moderate Irritant
	Placebo (negative control)	2.2	Moderate Irritant
	w/o-II (0.15% Retinol)	2.4	Moderate Irritant
	Placebo (negative control)	1.2	Mild Irritant

In general, the irritancy of topical formulation arises from both the active and the surfactants. The results in Table 9 show that 0.15% retinol w/o formulations, which contain approximately 2% surfactants, exhibit mild or marginally moderate irritancy. Surprisingly, 0.15% retinol non-phospholipid liposome formulations, which contain more than 8% surfactants, show similar irritancy as that of w/o formulation tested. The results suggest that non-phospholipid liposome formulations may have a potential to reduce the irritancy from the ingredients of the formulations.

EXAMPLE 11:

Evaluation of Cosmetic Performance:

Three non-phospholipid liposomal formulations and a water-in-oil emulsion (a stable retinol product marketed by RoC s.a,) containing 0.15% retinol were evaluated for quantitative descriptive analysis (QDA). The commercial product Night of Olay® from Procter & Gamble was used as a control. The objective of this evaluation was to determine the overall cosmetic attributes of the retin l creams. The evaluation was performed by a trained panel of scientists. The parameters which were evaluated were appearance in cup, feel between fingers, feel during application and skin feel after application.

The results for the various elements after application are shown in Figure 4 along with the same for Night of Olay for easy comparison. The results suggest that retinol liposome formulations were preferred over retinol in water-in-oil. The results also suggest that greasiness which is a big drawback for water-in-oil

emulsion can be controlled with slight modification of the liposomal formulation without compromising the stability of retinol. The results of comparisons of the formulations of Examples 6, 8 and two commercial compositions are set forth in Fig. 4.

According to above observations, the products of this invention unexpectedly provide chemical stability enhancement, bioavailability programmability of retinoids to the skin, as well as improvement of the cosmetic elegance of the vehicle, which can all be achieved in a single non-phospholipid liposome formulation.

WHAT IS CLAIMED IS:

1. A composition for skin care comprising a non-phospholipid liposome and a retinoid selected from the group consisting of retinol, retinal, retinyl acetate, retinyl palmitate and mixtures thereof, said composition further comprising a stabilizing system selected from the group consisting of:

a) an oil-soluble antioxidant; and

b) a chelating agent and at least one oil-soluble antioxidant;

wherein said composition has a pH from at least about 5 to about 10, said composition retaining at least 80% of said retinoids after 13 weeks' storage at 50°C.

2. A composition according to claim 1 wherein said retinoid is Vitamin A alcohol.

3. A composition according to claim 1 wherein said retinoid is Vitamin A acid.

4. A composition according to claim 1 wherein said retinoid is Vitamin A aldehyde.

5. A composition according to claim 1 wherein said oil-soluble antioxidant is selected from the group consisting of butylated hydroxytoluene,

ascorbyl palmitate, butylated hydroxyanisole, α-tocopherol, phenyl-α-naphthylamine and mixtures thereof.

6. A composition according to claim 1 wherein said chelating agent is selected from the group consisting of ethylenediamine tetraacetic acid and derivatives and salts thereof, dihydroxyethyl glycine, citric acid, tartaric acid, and mixtures thereof.

7. A composition according to claim 6 wherein said chelating agent is selected form the group consisting of ethylenediamine tetraacetic acid and derivatives and salts thereof.

8. A composition according to claim 1 wherein the pH of said composition is from about 5 to about 7.

9. A skin care composition comprising a non-phospholipid liposome and a retinoid selected from the group consisting of retinol, retinal, retinyl acetate, retinyl palmitate and mixtures thereof, said composition further comprising a stabilizing system comprising an oil-soluble antioxidant, wherein said composition has a pH from at least about 5 to about 10, said composition retaining at least 80% of said retinoids after 13 weeks' storage at 50°C.

10. A composition according to claim 9 wherein said oil-soluble antioxidant is selected from the group consisting of butylated hydroxytoluene,

ascorbyl palmitate, butylated hydroxyanisole, α-tocopherol, phenyl-α-naphthylamine and mixtures thereof.

11. A skin care composition comprising a non-phospholipid liposome and a retinoid selected from the group consisting of retinol, retinal, retinyl acetate, retinyl palmitate and mixtures thereof, said composition further comprising a stabilizing system comprising at least one oil-soluble antioxidant and a chelating agent, wherein said composition has a pH from at least about 5 to about 10, said composition retaining at least 80% of said retinoids after 13 weeks' storage at 50°C.

12. A composition according to claim 11 wherein said oil-soluble antioxidant is selected from the group consisting of butylated hydroxytolu ne, ascorbyl palmitate, butylated hydroxyanisole, α-tocopherol, phenyl-α-naphthylamine and mixtures thereof.

13. A composition according to claim 11 wherein said chelating agent is selected form the group consisting of ethylenediamine tetraacetic acid and derivatives and salts thereof, dihydroxyethyl glycine, citric acid, tartaric acid, and mixtures thereof.

14. A composition according to claim 9 wherein said retinoid is Vitamin A alcohol.

15. A composition according to claim 11 wherein said retinoid is Vitamin A alcohol.

16. A composition according to claim 9 wherein the pH is from about 5 to about 7.

17. A composition according to claim 11 wherein the pH is from about 5 to about 7.

Figure 1

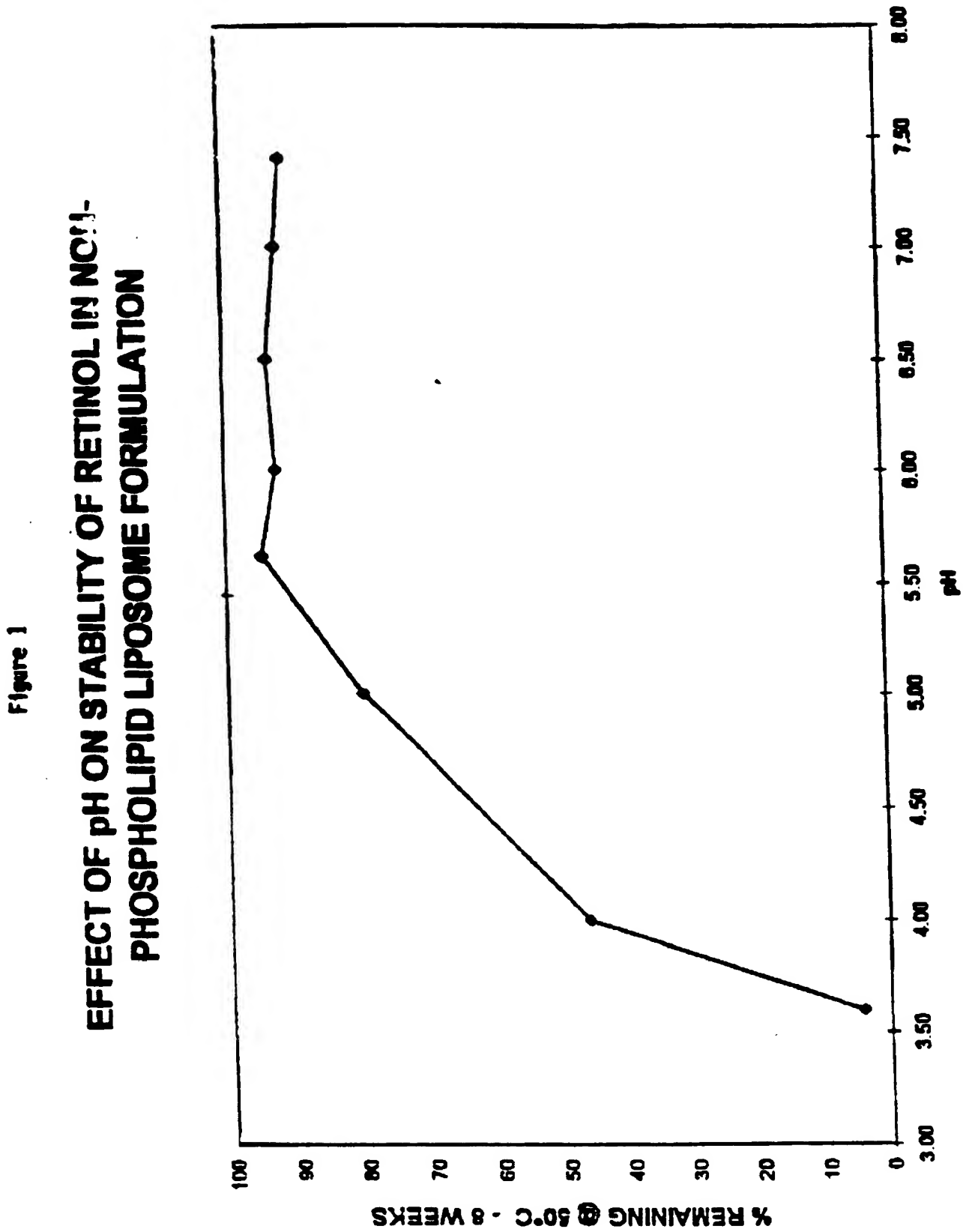

EFFECT OF pH ON STABILITY OF RETINOL IN NCI-
PHOSPHOLIPID LIPOSOME FORMULATION
% REMAINING @ 50°C - 8 WEEKS
100
90
80
70
60
50
40
30
20
10
0
3.00
3.50
4.00
4.50
5.00
5.50
6.00
6.50
7.00
7.50
8.00
pH

Figure 2

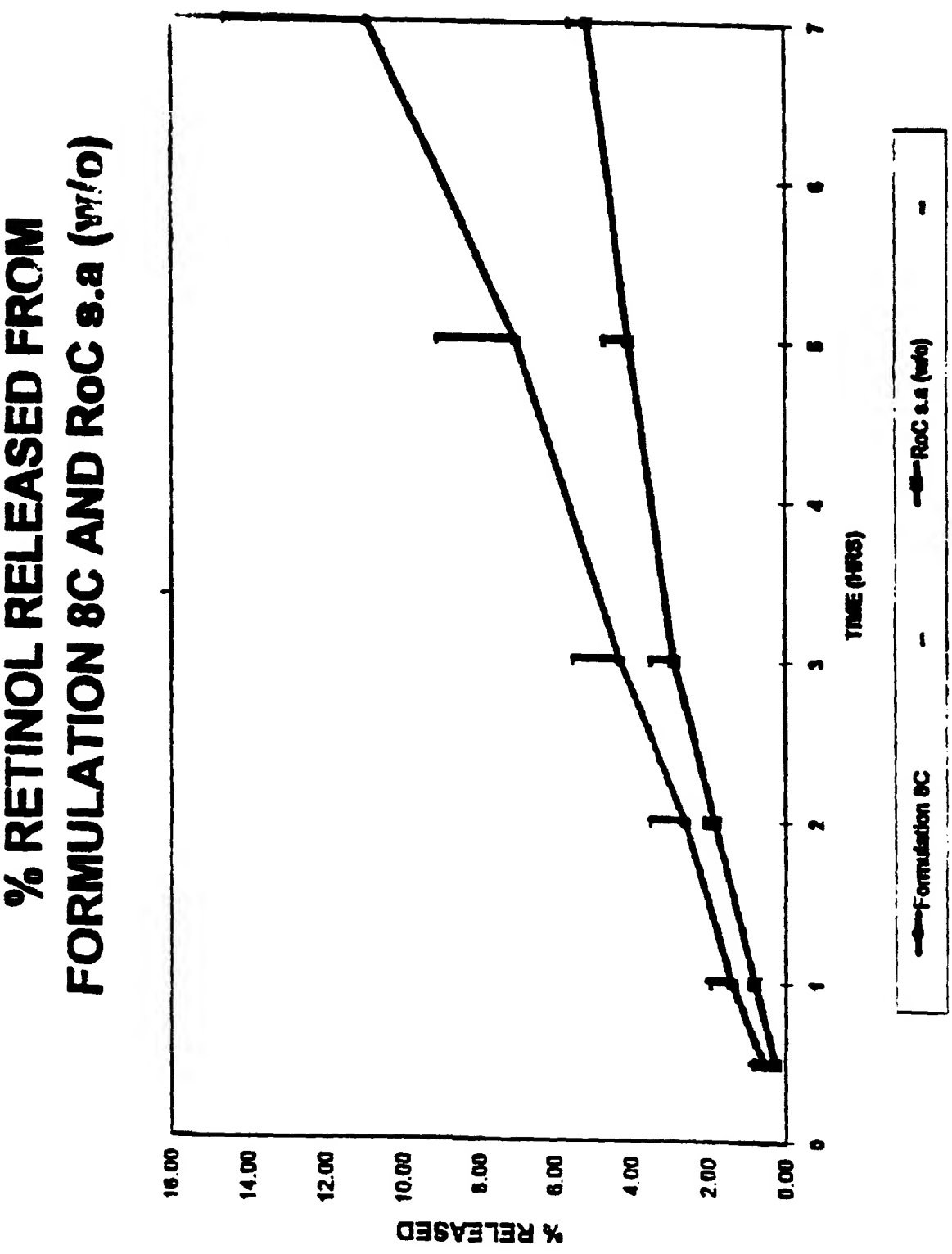


Figure 3

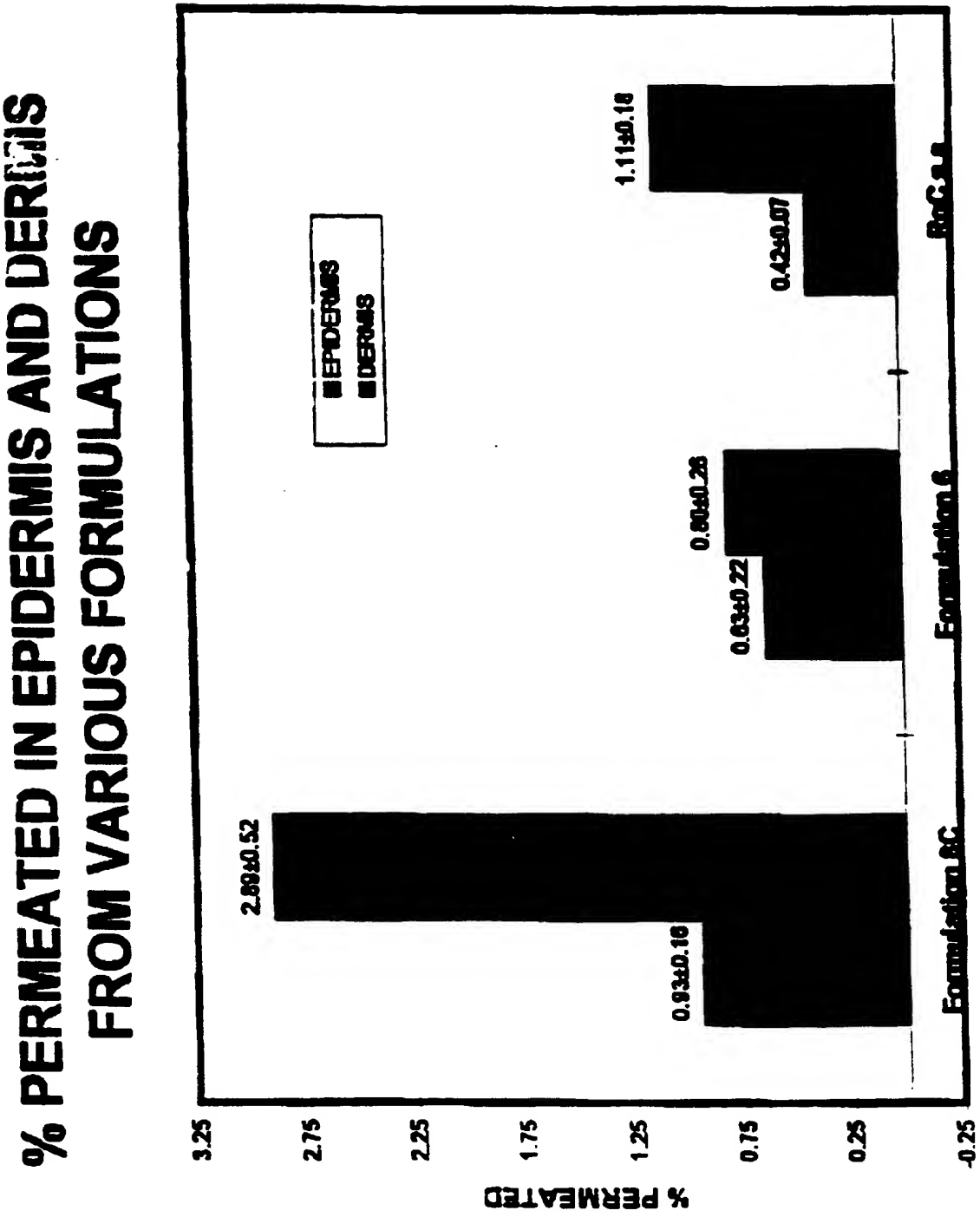
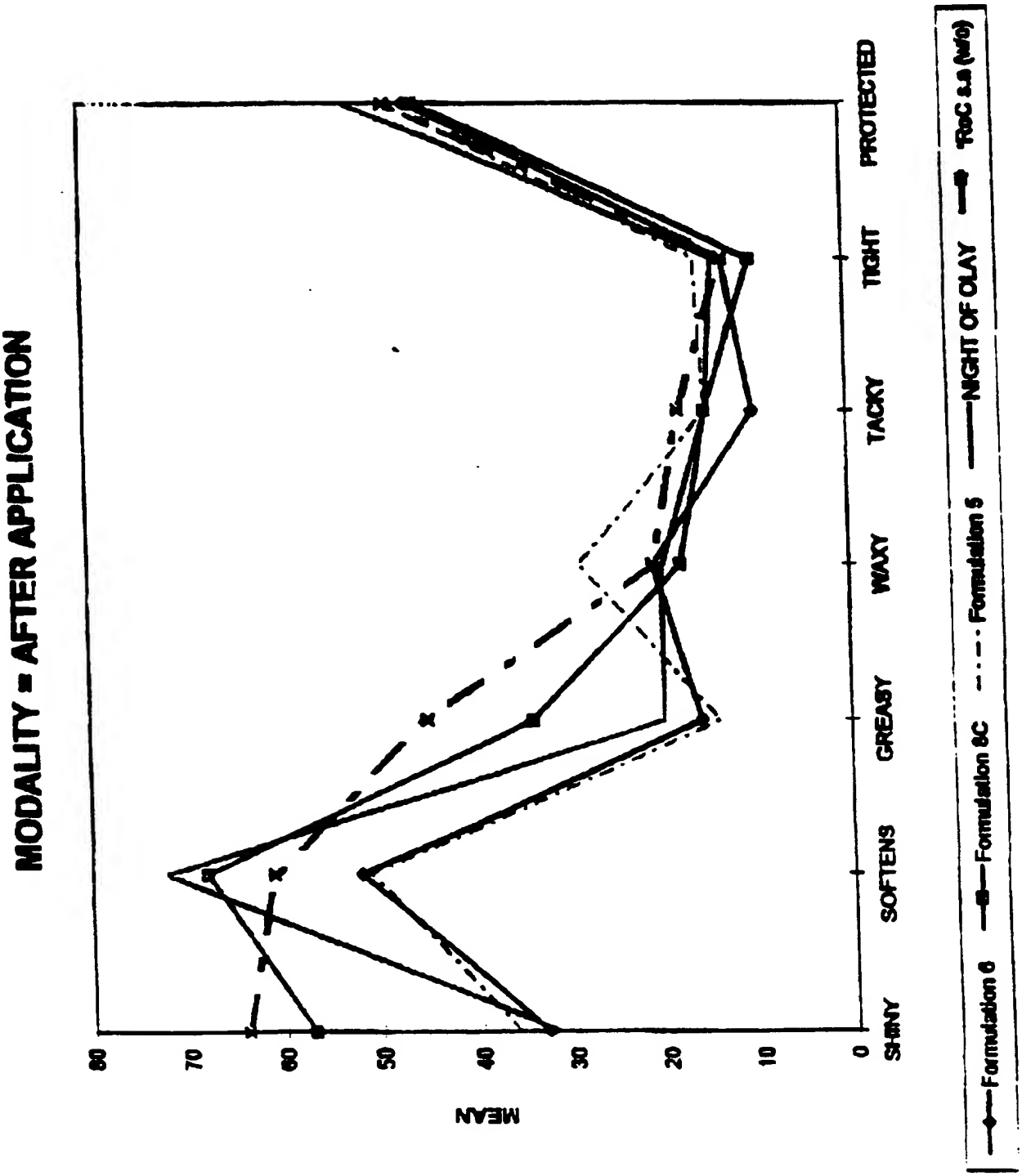


Figure 4



INTERNATIONAL SEARCH REPORT

International Application No
PCT/US 96/04557

A. CLASSIFICATION OF SUBJECT MATTER
IPC 6 A61K7/48

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
IPC 6 A61K

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	EP,A,0 423 011 (L'OREAL) 17 April 1991 see claims 1,3,9-13; example 5 -----	1-17

☐ Further documents are listed in the continuation of box C.

☒ Patent family members are listed in annex.

* Special categories of cited documents :

"A" document defining the general state of the art which is not considered to be of particular relevance

"E" earlier document but published on or after the international filing date

"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

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INTERNATIONAL SEARCH REPORT

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